Platelet-lymphocyte ratio in predicting mortality of patients in pediatric intensive care unit

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Abstract

Aim: Patients in the PICU have high rates of mortality. In this study we researched whether platelet-lymphocyte ratio (PLR), in addition to other scoring methods, is an early predictor of mortality risk in PICU patients. Material and Method: The patient files of children hospitalized in the PICU between 2014 and 2015 were examined. Results: A total of 670 patients were included (46.9% girls and 53.1% boys). 25 (3.7%) of these children died. In patients who died, the GCS was below 9, and PRISM, PELOD, and PIM2 scores were above 12, 7, and 90, respectively ($p<0.001$ for each factor). Significant cut-off values were 2 ($p<0.001$) for lactate (100% sensitivity, 64.3% specificity) and 3.9 ($p<0.001$) for PLR (80% sensitivity, 68.9% specificity). Diagnoses such as hematological-oncological diseases, sepsis, or multi-organ failure in children admitted to the PICU were factors affecting mortality ($p=0.001$, $p=0.008$, and $p<0.001$, respectively). Other factors affecting mortality were found to be high PIM2 scores ($p=0.041$), hyperlactatemia ($p<0.001$), and high PLR ($p<0.001$). Discussion: In addition to known scoring methods, PLR is a beneficial predictive factor of mortality rate in PICU patients.

Keywords

PLR, Intensive Care; Mortality; Child

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Introduction

Pediatric intensive care units (PICU) have special equipment for treatment of children with life-threatening conditions [1]. These patients' conditions may be due to a severe illness, poisoning, trauma, or unpredictable complications arising from surgery [2]. The main purpose of therapies in a PICU is supporting patients until the dysfunction heals by natural means or the toxic material or the infection is eliminated. Morbidity and mortality rates in patients admitted to the PICU are higher than in other pediatric patients, because of the worse clinical picture [1-3].

In our country, few studies have evaluated the findings of children treated in the PICU [1, 3-6]. Sharing the experience obtained from these studies may not only benefit the planning of educational programs but will also help to improve the health care services given in intensive care units [4].

In PICU patients with a severe clinical course, there are several markers that can reveal the severity of inflammation, but they are expensive and difficult to work with. Platelet-lymphocyte ratio (PLR) is a novel inflammatory marker. It has been shown that PLR can be used as a useful marker for early diagnosis [7, 8] and treatment of some diseases [9]. Also, it has been shown that PLR is a useful marker in predicting the prognosis of some diseases in adults [10, 11]. This study aimed to research whether PLR is a predictive factor of mortality risk in PICU patients.

Material and Method

Approval was granted from the local ethics committee. The files of patients treated in our hospital's PICU between January 2014 and December 2015 were retrospectively examined.

Children aged between 1 month and 18 years who were hospitalized in the PICU were included in the study. Patients' demographic data, causes for hospitalization, and laboratory findings were recorded. The Glasgow Coma Scale (GCS) was used to evaluate the level of consciousness of the patients at the time of admission to the PICU [12]. In addition, to determine if there is a worsening in the patient's condition and to assess the risk of mortality in the patients admitted to the PICU, pediatric risk of mortality (PRISM) [13] and pediatric index of mortality (PIM2) [14] scores were used, and pediatric logistic organ dysfunction (PELOD) score was used to evaluate dysfunctions of the organs [15]. The blood tests were performed in our laboratory upon the patient's admission to the hospital. Patients receiving immunosuppressive therapy were excluded from the study. Neutrophil/lymphocyte (NLR) and PLR were calculated from complete blood counts. Blood gas samples were taken from arteries or veins and a serum lactate level above 2 mmol/L was accepted as hyperlactatemia.

SPSS version 21.0 (IBM SPSS) and MedCalc 16 package software were used for statistical analyses. Findings were presented with mean ± SD. Categorical data was presented with numbers and percentages. Student's t test was used for the analysis of the continuous variables between two independent groups in the normally distributed data, and Mann Whitney U test was used where data was not normally distributed. Binary Logistic Regression analysis was conducted to find factors that affected mortality. The significance level was set at $p<0.05$.

To determine the threshold value for mortality, ROC (receiver operating characteristic) curve was used. The area under the ROC curve, and the points of specificity, sensitivity, and cut-off points were calculated with the MedCalc 16 package software. Youden Index was used to determine cut-off points.

Results

A total of 670 patients hospitalized in the PICU over the two-year period were included in the study, of whom 314 (46.9%) were girls and 356 (53.1%) were boys, and the average age was 5.2±5.4 years.

In total, 25 patients (3.7%) (9 girls (2.9%) and 16 boys (4.5%)) were non-survivors. There was no significant difference between the survivor and non-survivor patients as regards gender ($p=0.18$) or average age (5.1±5.3 years and 6.6±6 years) ($p=0.27$). 143 (22.2%) of survivor patients and 14 (56%) of non-survivor patients stayed in the PICU longer than the average duration, revealing another significant difference (OR:4.4, 95% CI (1.9-10), $p<0.001$). The duration of stay in the PICU and mortality were found to be significantly correlated ($p=0.04$). The deaths were due to cardiovascular (52%), pulmonary (44%), and neurological (4%) causes.

Reasons for hospitalization in the PICU were accidents and poisoning in 226 (33.7%) patients, respiratory system diseases in 192 (28.6%), central nervous system diseases in 152 (22.6%), cardiovascular system diseases in 32 (4.7%), hematological-oncological diseases in 7 (1%), and other diseases in 61 (8.6%). When compared to survivor patients, non-survivor patients had significantly higher rates of sepsis (5% vs. 68%, $p<0.001$), shock (1% vs. 28%, $p<0.001$), multi-organ failure (2% vs. 76%, $p<0.001$), and renal failure (1% vs. 28%, $p<0.001$) (Table 1).

Table 1. The distribution of diagnoses between survivor and non-survivor patients

Secondary diagnoses	Survivor patients (n= 645)		Non-survivor patients (n= 25)		p
	Not found	Found	Not found	Found	
Sepsis	613(95%)	32(5%)	8(32%)	17(68%)	<0.001
Shock	640(99%)	5(1%)	18(72%)	7(28%)	<0.001
Multi-Organ Failure	638(98%)	7(2%)	6(24%)	19(76%)	<0.001
Renal Failure	640(99%)	5(1%)	18(72%)	7(28%)	<0.001

It was found that survivor patients and non-survivor patients differed significantly in lymphocyte ($p=0.015$), RDW ($p=0.023$), platelet ($p=0.037$), NLR ($p=0.037$) and PLR (10.5±34.9 vs. 63±133.1, $p<0.001$), blood glucose ($p=0.009$), urea ($p=0.011$), AST ($p<0.001$), ALT ($p=0.026$), sodium ($p<0.001$), calcium ($p<0.001$), CRP ($p=0.001$), albumin ($p<0.001$), pH $p=0.004$), HCO3 ($p=0.006$), and lactate ($p<0.001$) (Table 2).

Patients' score were as follows: Glasgow Coma Score 12.1±2.6, PRISM 3.5±7.9, PELOD 1.6±5.6, and PIM2 7.1±24.5. GCS was below the level of 9 in 43 (6.7%) of the survivor patients and 21 (84%) of the non-survivor patients, so the difference between the two groups was significant (OR: 73.5). 26 (4%) of the survivor patients and 23 (92%) of the non-survivor patients had PRISM score above 12, indicating another significant difference (OR: 273). The number of patients with a PELOD score greater than 7 was significantly higher in the non-survivor pa-

tients compared to the survivor patients (96% vs 3.6%) (OR: 649). The number of non-survivor patients with a PIM2 score above 90 was significantly greater than the survivor patients (100% vs 2.1%) (OR:3.2). Serum albumin level was found to be lower than 3.4 in 5 (29.9%) of the survivor patients and in 16 (76.2%) of the non-survivor patients, which indicated another significant difference (OR:7.5). Another significant difference was the rate of hyperlactatemia, which was present in 20 survivor patients (11.5%) and 16 non-survivor patients (94.7%) (OR:138) (Table 3). The PLR cut-off value that predicts mortality was found to be 3.9 (Figure 1). The number of patients with PLR values above 3.9 differed significantly between the two groups, with 200 survivor (31%) and 19 non-survivor patients (76%) (AUC: 0.75, OR:7, 95% CI (2.7-17.9), p<0.001) (sensitivity 80%, specificity 68.9%). No statistically significant difference was found between the two groups as regards NLR (p=0.077). Diagnoses such as hematological-oncological diseases (p=0.001), sepsis (p=0.008), and multi- organ failure (p<0.001) were found to contribute to mortality rates. The presence of a high PIM2 score was detected to be related to high rates of mortality (p=0.041). The other findings to contribute to mortality were low albumin levels (p=0.006), hyperlactatemia (p<0.001), and high PLR (95% CI (1.004-1.013), p<0.001) (Table 4).

Table 2. Comparison of the laboratory findings of the survivor and non-survivor patients

	Survivor patients (n= 645)	Non-survivor patients (n= 25)	p value
WBC(K/uL)	11.2±5.6x10³	11.3±7.5 x10³	0.89
Neutrophil(K/uL)	7.4±17.5 x10³	8.4±6.8 x10³	0.79
Lymphocyte(K/uL)	3.3±2.1 x10³	2.2±2.2 x10³	0.015
MPV(fl)	8±1.2	8±1.4	0.66
RDW(%)	15.3±2.4	16.5±2.8	0.023
PLT(K/uL)	317.3±123.47 x10³	276.8±199.46 x10³	0.037
HGB(g/dl)	12±1.8	11.2±2.4	0.05
NLR	3.5±6.8	5.8±5.7	0.037
PLR	10.5±34.9	63±133.1	<0.001
BG(mg/dl)	103.5±43.5	199.4±187.2	0.009
Urea(mg/dl)	21.3±13.6	34.2±25.8	0.011
Creatinine(mg/dl)	0.4±0.1	0.7±1	0.067
AST(IU/l)	45.3±79.8	188.4±350.8	<0.001
ALT(IU/l)	27.9±57.1	105.9±257.4	0.026
Sodium(mEq/l)	136.6±3.5	133.8±5.5	<0.001
Potassium(mmol/l)	4.4±0.6	4.2±1.4	0.106
Chloride(mEq/l)	104.3±5.1	101.5±8.8	0.004
Calcium(mg/dl)	9.3±0.7	8.5±1.1	<0.001
Phosphorus(mg/dl)	4.6±3.2	3.7±2.5	0.001
CRP(mg/dl)	17.5±38.6	57.5±94.8	0.001
Albumin(g/dl)	3.7±0.7	3±0.7	<0.001
pH	7.35±0.09	7.24±0.18	0.004
pCO_2(mmHg)	38.7±12.4	38.9±13.6	0.555
HCO_3(mmol/l)	20.7±4.8	16.4±7.3	0.006
Lactate(mmol/l)	2.1±1.8	4.4±4.2	<0.001

WBC: White Blood Cell, MPV: Mean Platelet Volume, RDW: Red Cell Distribution Width, PLT: Platelet, HGB: Hemoglobin, NLR: Neutrophil Lymphocyte Ratio; PLR: Platelet-Lymphocyte Ratio; CRP: C-reactive protein; MPV: Mean Platelet Volume, BG: Blood Glucose; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase

Table 3. Comparison of the values of parameters that can be used for predicting mortality

Parameters	Cut-off value	Found in Survivor*	Found in non-survivor*	Sensitivity	Specificity	OR	p	95% CI
GCS	< 9	6.7	84	96	91	73.5	<0.001	24.1-223.7
PELOD	>7	3.6	96	100	96.1	649	<0.001	84.1-5007.5
PIM2	> 90	2.1	100	100	98.2	3.2	<0.001	2-5.3
PRISM	> 12	4	92	96	94.8	273	<0.001	61.1-1221.6
Albumin	<3.4	29.9	76.2	76.1	70.1	7.5	<0.001	2.5-21.8
Lactate	>2	11.5	94.7	100	64.3	138	<0.001	17.5-1094.9
PLR	>3.9	31	76	80	68.9	7	<0.001	2.7-17.9

GCS: Glasgow Coma Scale, PRISM: Pediatric Risk of Mortality, PIM: Pediatric Index of Mortality, PELOD: Pediatric Logistic Organ Dysfunction, PLR: Platelet-Lymphocyte Ratio; *:%, AUC: Areas under the ROC curve, OR: Odds ratio

Table 4. Findings of the regression analysis of risk factors affecting mortality

Parameters	B	S.E.	Sig.	Exp(B)	95% CI	Lower Upper
Hematological-Oncological disease	3.65	1.11	0.001	38.6	4.3	345.5
Sepsis	1.92	0.72	0.008	6.8	1.6	28.1
Multi-Organ Failure	5.56	0.76	<0.001	260.7	1.1	57.9
PIM2	0.21	0.106	0.041	1.2	1.009	1.5
Albumin	-1.55	0.56	0.006	0.21	0.07	0.63
Hyperlactatemia	4.93	1.05	<0.001	138.6	1.095	17.5
PLR	0.009	0.002	<0.001	1.009	1.004	1.013

PIM: Pediatric Index of Mortality, PLR: Platelet-Lymphocyte Ratio

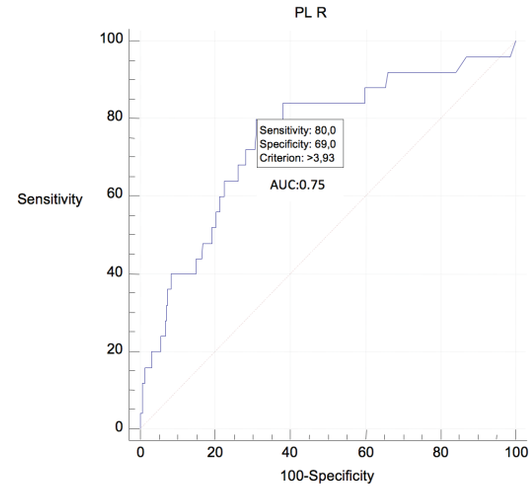

Figure 1. ROC Curve of PLR Predicting Mortality

Discussion

Morbidity and mortality levels differ in patients admitted to the PICU due to their clinical status [2]. The studies performed on these units basically aim to decrease morbidity and mortality rates. However, despite all the progress made, the mortality rates have not yet been brought down to the target levels [1]. The mortality rates in PICUs worldwide vary between 2.9% and 5.6% [16-19]. These rates have decreased from 14% to 2.4-8.8% in developed countries [3, 4]. We found a mortality rate of

3.7%, which is similar to the world average. This may indicate an improvement in the quality of health services in our unit.

Sensitivity and specificity of the following factors were found to be high for predicting mortality: GCS score below 9, PELOD score greater than 7, PIM score over 90, and PRISM score above 12. 84% of cases with a GCS score lower than 9, 96% of those with PELOD score over 7, 100% of those with PIM2 score over 90, and 92% of those with PRISM score over 12 resulted in death.

In our study, a high PIM2 score was a factor increasing mortality rate 1.2 fold. Our findings suggest that these scores need to be monitored closely, particularly in patients hospitalized in the PICU. Because of the remarkable relation between mortality rates and high rates of the above-mentioned scoring systems, treatments need to be aimed at keeping markers related to those scoring systems under control.

A study reported that hematological diseases and renal failure occur more commonly in cases that result in death while being followed up in the PICU [5]. We found multi-organ failure in 3.8% of all cases and in 76% of non-survivor patients. The mortality of patients hospitalized in the PICU is related to the number of impaired organs. The frequency of multi-organ failure is 11-18% in these patients, with a death rate of 50% [20, 21].

Shock and renal failure were found in 1.7% of our cases, and each disorder was mortal in 28% of cases. Sepsis was present in 7.3% of cases, and 68% of these cases were mortal. We found sepsis, hematological-oncological diseases, and multi-organ failure to increase mortality by 6.8, 38.6, and 260.7 fold, respectively. Patients with such diseases need to be monitored closely against mortality, and necessary precautions need to be taken to prevent death.

We found hyperlactatemia and low serum albumin levels to be significant predictors of mortality. Because albumin is a marker for nutritional status, inflammatory response, and the severity of the disease, low serum albumin values are believed to be a significant factor for increased morbidity and mortality in children followed up in the PICU [22]. We detected hypoalbuminemia in 27.2% of the patients, and in 61.9% of those it led to a mortal condition; thus, hypoalbuminemia increased mortality by 0.2 fold. Serum lactate level shows tissue oxygenation, and may guide in determining prognosis in children with critical disorders [23]. We found hyperlactatemia in 19.6% of the all cases, and in 94.7% of the cases that resulted in death, meaning that hyperlactatemia caused a 138.6 fold increase in mortality. When evaluating blood gas findings, particular attention needs to be paid to lactic acid values, as high amounts may increase the risk of mortality.

Inflammation, which is a crucial function of the inherent immune system, is a physiological process occurring as a response to tissue damage arising from infections, toxins, or trauma. When tissue damage occurs in the human body, the immune system activates neutrophils, leukocytes, lymphocytes, and other inflammatory cells [24]. Neutrophils initiate a non-specific inflammatory response whereas lymphocytes regulate more specific response by producing antibodies against foreign materials. The count of these cells varies depending on the cytokines during inflammation [25, 26].

There are various methods to predict the survival of patients admitted to the PICU, including clinical and laboratory findings, some of which may be related to patients' previously occuring metabolic processes. However, PLR and NLR are simple and useful indicators of the inflammatory process that has developed shortly before admission.

NLR, a simple parameter, can be used to predict severity of inflammation [27] as well as prognosis [28]. Mortality rates were reported to be higher in patients with high NLR levels hospitalized in the PICU [29]. We found high levels of NLR in non-survivor patients, in line with the literature. However, we could not identify NLR as a marker of mortality risk.

The increase in platelets during inflammation or infection [30] is caused by cytokines [31]. Another simple parameter, PLR, can be used to predict severity of inflammation and prognosis [32]. PLR and mortality are correlated; patients with high PLR ratios were found to have high mortality rates [33]. We found high PLR ratios in non-survivor patients in our study, and the cut-off value of 3.93 indicated increased mortality (sensitivity 80%, specificity 68.9%). We also found that high PLR levels alone can predict higher risk of mortality.

Study Limitations

The major limitations of our study are that it was retrospective and the small number of patients. Further investigations with larger and stratified samples are needed.

Conclusions

High PIM2 score and hyperlactatemia can be used as predictors of mortality in PICU patients. Also, the cut-off value of 3.9 for PLR has high sensitivity and medium specificity of predicting mortality risk. PLR is a simple parameter that can be used in predicting mortality risk of PICU patients.

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Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Abant Izzet Baysal University.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

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